

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
24 July 2003 (24.07.2003)

PCT

(10) International Publication Number  
**WO 03/059973 A3**

(51) International Patent Classification<sup>7</sup>: **C08F 293/00**,  
A61K 31/00, C08F 20/36, 4/00

(21) International Application Number: PCT/GB02/05932

(22) International Filing Date:  
27 December 2002 (27.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0131112.5 31 December 2001 (31.12.2001) GB

(71) Applicant (for all designated States except US): **POLY-  
THERICS LIMITED** [GB/GB]; 90 Fetter Lane, London  
EC4A 1JP (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BROCCHINI, Steve**  
[US/GB]; 15, Westly Wood, Welwyn Garden City, Hert-  
fordshire AL7 1QN (GB). **GODWIN, Antony** [GB/GB];  
159 St Peters Rise, Headley Park, Bristol BS13 7QR (GB).

(74) Agents: **SCOTT, Susan, Margaret** et al.; Abel & Imray,  
20 Red Lion Street, London WC1R 4PQ (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,  
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,  
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

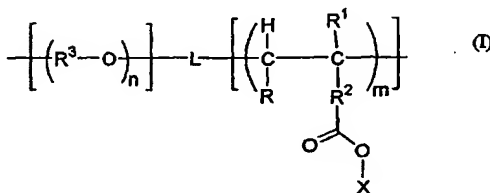
**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(88) Date of publication of the international search report:  
18 September 2003

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: BLOCK COPOLYMERS



(57) Abstract: Novel block copolymers are described, together with the production therefrom of physiologically soluble polymer therapeutics. The block copolymers have the general formula (1) wherein R is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>18</sub> alkyl, C<sub>2</sub>-C<sub>18</sub> alkenyl, C<sub>7</sub>-C<sub>18</sub> aralkyl, C<sub>7</sub>-C<sub>18</sub> alkaryl, C<sub>6</sub>-C<sub>18</sub> aryl, carboxylic acid, C<sub>2</sub>-C<sub>18</sub> alkoxycarbonyl, C<sub>2</sub>-C<sub>18</sub> alkaminocarbonyl, or any one of C<sub>1</sub>-C<sub>18</sub> alkyl, C<sub>2</sub>-C<sub>18</sub> alkenyl, C<sub>7</sub>-C<sub>18</sub> aralkyl, C<sub>7</sub>-C<sub>18</sub> alkaryl, C<sub>6</sub>-C<sub>18</sub> aryl, C<sub>2</sub>-C<sub>18</sub> alkoxycarbonyl and C<sub>2</sub>-C<sub>18</sub> alkaminocarbonyl substituted with a heteroatom within, or attached to, the carbon backbone; R<sup>1</sup> is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl groups; R<sup>2</sup> is a linking group; X is an electron withdrawing group; R<sup>3</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>18</sub> alkylene, C<sub>2</sub>-C<sub>18</sub> alkenylene, C<sub>7</sub>-C<sub>18</sub> aralkylene, C<sub>7</sub>-C<sub>18</sub> alarylene and C<sub>6</sub>-C<sub>18</sub> arylene; L is a divalent linker joining the blocks; and m and n are each an integer of greater than 1.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/05932

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08F293/00 A61K31/00 C08F20/36 C08F4/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08F C08L A61K C08G C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 18080 A (BROCCHINI STEPHEN JAMES ;GODWIN ANTONY (GB); UNIV LONDON PHARMACY) 15 March 2001 (2001-03-15) cited in the application * page 18, line 9-10, 14-15 (particularly polyethylene glycol) ; page 26, line 8-9 ; claims 1-38 ; examples * page 17, line 7 -page 28, line 15 ---	1-7,11
X	US 6 235 813 B1 (SILBER STEFAN ET AL) 22 May 2001 (2001-05-22) * claim 1 ; column 3, line 25 ; column 2, line 40 - column 3, line 29 ; claims 9, 2-19 ; examples * column 5, line 66 -column 6, line 57 --- -/--	1-7,11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

4 April 2003

Date of mailing of the International search report

30. 07. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hammond, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/05932

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 248 839 B1 (KNEBELKAMP ARNO ET AL) 19 June 2001 (2001-06-19) * claim 1 ; column 2, line 25 - column 4, line 8 ; examples * ---	1-7,11
X	WO 01 17515 A (BROCCHINI STEVEN JAMES ;CLOCHARD MARIE CLAUDE DUBOIS (GB); UNIV LO) 15 March 2001 (2001-03-15) * claims 8, 9, 17-22, 1-16 ; page 9, line 19 - page 23, line 10 ; examples * ---	1-7,11
A	DE 31 31 848 A (GOLDSCHMIDT AG TH) 24 February 1983 (1983-02-24) abstract; claims 1-12 ---	1-7,11
A	US 6 162 882 A (MATYJASZEWSKI KRZYSZTOF ET AL) 19 December 2000 (2000-12-19) * column 1, line 25-28 ; column 2, line 65 - column 3, line 8 ; column 9, line 36-38* column 7, line 48 -column 18, line 20 ---	1-7,11
A	US 5 763 548 A (MATYJASZEWSKI KRZYSZTOF ET AL) 9 June 1998 (1998-06-09) * column 6, line 30 ; column 6, line 37 - column 31, line 45 * column 3, line 33-54 ---	1-7,11
A	DE 195 20 875 A (BASF CORP) 14 December 1995 (1995-12-14) * abstract ; claim 1 * page 2, line 58 -page 4, line 20 ---	1-7,11
A	WO 00 55218 A (CALIFORNIA INST OF TECHN) 21 September 2000 (2000-09-21) * page 2, line 19 - page 3, line 7 * page 11, line 20-22; claims 1-33 ---	1-7,11
A	US 6 174 953 B1 (HUYBRECHTS JOSEF) 16 January 2001 (2001-01-16) * claims 1-5 * column 2, line 26 -column 4, line 31 ---	1-7,11
A	US 6 124 411 A (MATYJASZEWSKI KRZYSZTOF ET AL) 26 September 2000 (2000-09-26) * claims 1-16 * the whole document ---	1-7,11
A	WO 99 39731 A (SUPRATEK PHARMA INC ;ALAKOV VALERY Y (CA); BATRAKOVA ELENA V (US);) 12 August 1999 (1999-08-12) claims 1-21 -----	1-7,11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 02/05932

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7, 11

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,11

A block copolymer comprising the unit (I) :  

$$-(R_3-O)_n-L-(-(CHR-CR_1(R_2COOX)-)_m)-\dots(I)$$
, wherein m, n, L, X, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are as described in the application claim 1.

2. Claims: 8,9,10

A further specific block copolymer related to the general block copolymer formula (I) according to any one of the preceding claims, but wherein R<sub>2</sub> is specifically defined as described in application claims 8-10.

3. Claim : 11

A further specific block copolymer related to the general block copolymer formula (I) according to any one of the preceding claims, but wherein R<sub>3</sub> is specifically defined as described in claim 11.

4. Claim : 12

A further specific block copolymer related to the general block copolymer formula (I) according to claim 11, but wherein all R<sub>3</sub> groups are the same and are preferably all 1,2-ethylene or 1,2-propylene.

5. Claims: 13,14

A further specific block copolymer related to the general block copolymer formula (I) according to any one of the preceding claims, but wherein L is specifically defined as described in claims 13,14.

6. Claim : 15

A further specific block copolymer related to the general block copolymer formula (I) according to claim 14, but wherein L comprises a COR<sub>a</sub> group, wherein R<sub>a</sub> is specifically defined as described in claim 15.

7. Claims: 16-22

A further block copolymer comprising the structure (II) related to the general block copolymer formula (I), but

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

which comprises as the structure (II) :  

$$-(R7-O)_n-L1-(-(CHR12-CR13(R14COZ))-)_m-(-(CHR4-CR5(R6COQ))-)_p- \dots (II)$$
 , wherein the various components are as described in application claim 16.

## 8. Claims: 23-32

A process for the production of a block copolymer, comprising the polymerisation of ethylenically unsaturated monomers including a compound of structure (III) as described in claim 23.

## 9. Claim : 33

A process for the production of a block copolymer comprising the steps as described in claim 33, of polymerising ethylenically unsaturated monomers comprising a compound (VIII) as described in claim 33.

## 10. Claim : 34

A specific process related to claim 23 or claim 33, but wherein the ethylenically unsaturated monomer compound is specifically structure (XIII) as described in claim 34, and the initiator is specifically structure (XIV) as described in claim 34.

## 11. Claim : 35

A specific process related to claim 34, but wherein the copolymer is further reacted with a compound :  
 $H_2N-Gly-Len-Phe-Gly-Doxorubicin$ ,  
 then followed by a further process step in which the product of the above reaction is further reacted with 2-hydroxy-propylamine.

## 12. Claim : 36

A specific block copolymer related to the general block copolymer formula (I), but wherein the block copolymer has the specific structure (XII) as described in claim 36.

## 13. Claim : 37

A further block copolymer which is obtainable by reacting the block copolymer of claim 36 and a reagent selected to provide a pendant group comprising an aminoacyl linker or a cis-aconityl linker and a bioactive agent.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/05932

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0118080	A	15-03-2001	AU	7025600 A	10-04-2001
			EP	1222217 A1	17-07-2002
			WO	0118080 A1	15-03-2001
			JP	2003508606 T	04-03-2003
-----					
US 6235813	B1	22-05-2001	DE	19836253 C1	23-12-1999
			DE	59901597 D1	11-07-2002
			EP	0979844 A2	16-02-2000
-----					
US 6248839	B1	19-06-2001	DE	19705470 A1	27-08-1998
			DE	59801101 D1	06-09-2001
			EP	0859028 A2	19-08-1998
			ES	2162353 T3	16-12-2001
-----					
WO 0117515	A	15-03-2001	AU	7346400 A	10-04-2001
			EP	1210093 A1	05-06-2002
			WO	0117515 A1	15-03-2001
-----					
DE 3131848	A	24-02-1983	DE	3131848 A1	24-02-1983
			CH	653691 A5	15-01-1986
-----					
US 6162882	A	19-12-2000	US	6111022 A	29-08-2000
			US	5945491 A	31-08-1999
			US	5789487 A	04-08-1998
			US	6124411 A	26-09-2000
			AU	3585997 A	02-02-1998
			BR	9710273 A	10-08-1999
			CA	2259995 A1	15-01-1998
			CN	1228789 A	15-09-1999
			EP	0914352 A1	12-05-1999
			JP	2000514479 T	31-10-2000
			KR	2000023686 A	25-04-2000
			TW	397852 B	11-07-2000
			WO	9801480 A1	15-01-1998
-----					
US 5763548	A	09-06-1998	AU	720512 B2	01-06-2000
			AU	5306996 A	16-10-1996
			BR	9604887 A	30-11-1999
			CA	2216853 A1	03-10-1996
			CN	1183107 A	27-05-1998
			EP	0817806 A1	14-01-1998
			JP	3040172 B2	08-05-2000
			JP	10509475 T	14-09-1998
			US	6407187 B1	18-06-2002
			WO	9630421 A1	03-10-1996
			US	2002193538 A1	19-12-2002
			US	6512060 B1	28-01-2003
			US	6541580 B1	01-04-2003
-----					
DE 19520875	A	14-12-1995	DE	19520875 A1	14-12-1995
			US	5562912 A	08-10-1996
-----					
WO 0055218	A	21-09-2000	AU	3632300 A	04-10-2000
			EP	1169364 A1	09-01-2002
			JP	2002539299 T	19-11-2002
			WO	0055218 A1	21-09-2000
			US	2003013825 A1	16-01-2003
			US	6410666 B1	25-06-2002

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/05932

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6174953	B1	16-01-2001	US 6157864 A	05-12-2000
			AU 2682699 A	06-09-1999
			BR 9908134 A	05-12-2000
			EP 1054915 A1	29-11-2000
			WO 9942505 A1	26-08-1999
-----				
US 6124411	A	26-09-2000	US 6111022 A	29-08-2000
			US 5945491 A	31-08-1999
			US 5789487 A	04-08-1998
			US 6162882 A	19-12-2000
			AU 3585997 A	02-02-1998
			BR 9710273 A	10-08-1999
			CA 2259995 A1	15-01-1998
			CN 1228789 A	15-09-1999
			EP 0914352 A1	12-05-1999
			JP 2000514479 T	31-10-2000
			KR 2000023686 A	25-04-2000
			TW 397852 B	11-07-2000
			WO 9801480 A1	15-01-1998
-----				
WO 9939731	A	12-08-1999	US 6277410 B1	21-08-2001
			AU 2496199 A	23-08-1999
			CA 2319057 A1	12-08-1999
			EP 1053010 A1	22-11-2000
			JP 2002502825 T	29-01-2002
			WO 9939731 A1	12-08-1999
			US 6387406 B1	14-05-2002
-----				